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## (54) THICKENER FOR CONTRAST MEDIUM

(57)Abstract:

PROBLEM TO BE SOLVED: To provide a thickener which is useful for contact media and can be added to the contact media to give viscous or gelled contact media that scarcely change the viscosities with the passage of time and have constant viscosities between the production time and employment time of the contact media, by dissolving a paste in water to prepare a flowable liquid.

SOLUTION: This thickener is produced by dissolving a paste such as guar gum, locust bean gum, Tara gum, xanthan gum, tamarind gum or tragacanth gum in water to form a viscous liquid. The paste is preferably dissolved in water together with a low viscous polysaccharide (for example, gum, arabic, arabinogalactan, pullulan or soybean polysaccharide) or the expression of prate viscosity is suppressed to give a flowable liquid. The thickener is added to a contrast medium (for example, iopamidol, iohexol or ferric ammonium citrate) to give the viscous or gelled contrast medium.

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## CLAIMS

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[Claim(s)]

[Claim 1] A thickener for contrast media which is a thickener for contrast media prepared as a fluid which dissolves a thickening agent in water and is liquid, and is characterized by viscosity or gelling being revealed by adding to a contrast medium.

[Claim 2] The thickener for contrast media according to claim 1, wherein said thickener for contrast media is prepared as a fluid which is liquid by preparing dissolved concentration of a thickening agent or controlling a viscous manifestation of a thickening agent.

[Claim 3] The thickener for contrast media according to claim 1, wherein said thickener for contrast media is prepared as a fluid which is liquid by using a thickening agent together with gum arabic, arabinogalactan, pullulan, and low viscosity polysaccharide selected from soybean polysaccharides, and dissolving in water.

[Claim 4] The thickener for contrast media according to claim 1, wherein said thickener for contrast media is adjusted as a fluid which is liquid by making a thickening agent and existing reactant ion contain, and controlling a viscous manifestation.

[Claim 5] The thickener for contrast media according to claim 1, wherein said thickener for contrast media is adjusted as a fluid which is liquid by using low-molecular sugar together and dissolving a thickening agent in water.

[Claim 6] Said thickening agent Guar gum, locust bean gum, tara gum, xanthan gum, Tamarind gum, tragacanth gum, karaya gum, konjak mannan, CMC sodium, sodium alginate, pectin, azotobacter BINDERANJIGAMU, Carrageenan, agar, gellant gum, furcellaran, gelatin, curdlan, modified starch, cassia gum, a psyllium seed gum, CMC, the thickener for contrast media according to any one of claims 1 to 5 characterized by a thing selected from methyl cellulose which is a kind at least.

[Claim 7] The thickener for contrast media according to any one of claims 1 to 6, wherein said thickener for contrast media is a thing as for which below equivalent weight adds to said contrast medium and which makes viscosity reveal.

[Claim 8] The thickener according to any one of claims 1 to 7, wherein said thickener is subdivided into either a portion container or a small bag.

[Claim 9] The thickener according to claim 1 being a thing which said thickener is divided and prepared for the first liquid and the second liquid, adds these first liquid and second liquid to a contrast medium, and makes viscosity reveal by an interaction of the first liquid and the second liquid.

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## DETAILED DESCRIPTION

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[Detailed Description of the Invention]

[0001]

[Field of the Invention] This invention relates to the thickener for contrast media which makes the contrast medium for swallowing function diagnosis reveal viscosity or gelling.

[0002]

[Description of the Prior Art] From the former, in order to make a decision of the existence of a swallowing difficulty, a grade, or a meal gestalt, diagnosis of the grade a test subject's swallowing function is performed. Although a test subject is made to take the fluid which distributed barium sulfate in water as a diagnosing method of a swallowing function and there is a method of observing signs that the dispersion liquid pass the esophagus, through X-rays, Since the above-mentioned barium sulfate dispersion liquid are a sol state, when the test subject to whom the swallowing function fell takes, when the patient to whom a swallowing reflex did not happen easily, therefore elderly people and a swallowing function fell takes barium sulfate dispersion liquid, he has a risk of dispersion liquid being attracted by endotracheal incorrect and suffocated with it with pain.

[0003] Then, since it is generally known that a solid will tend to start a swallowing reflex than a liquefied substance, the gel contrast medium near a solid is used for diagnosis of a swallowing function instead of being a contrast medium of the hydrosol. Diagnosis of the swallowing function which uses a gel contrast medium is performed by changing the viscosity of the contrast medium prescribed for the patient. As a gel contrast medium used for diagnosis of a swallowing function, there are some which are changed into a gelling state, for example by adding powdered thickeners, such as pregelatinized starch, to contrast media, such as barium sulfate (JP,6-65106,A).

[0004]

[Problem(s) to be Solved by the Invention] However, the contrast medium which added the powdered thickener and was changed into the gelling state, The stability with time of the viscosity is bad, and since the viscosity at the time of preparation and use changes in a deglutition imaging inspection, the danger of being unable to perform an exact inspection, and pain being attracted by the test subject, and dispersion liquid being attracted by endotracheal incorrect, and being suffocated may be given.

[0005] Then, an object of this invention is to provide the thickener for contrast media

which can reveal viscosity or gelling so that the change with time of the viscosity of the contrast medium which changed into the gelling state may decrease.

[0006]

[Means for Solving the Problem]Viscosity or gelling reveals this invention by being the thickener for contrast media prepared as a fluid which was made in order to attain the above purpose, dissolves a thickening agent in water, and is liquid, and adding to a contrast medium. A thickener concerning this invention is prepared as a liquid fluid by preparing dissolved concentration of a thickening agent or controlling a viscous manifestation of a thickening agent.

[0007]As mentioned above, according to this invention, since a thickener for contrast media is prepared as a liquid fluid, when it adds to a contrast medium, it cannot form lumps like [ in the case of powder ], and the whole contrast medium can be distributed easily. According to this invention, since viscosity or gelling is revealed by adding to a contrast medium, there are few changes with time of viscosity of a contrast medium after being able to cover the whole contrast medium, being able to give viscosity and gelling and viscosity or gelling being revealed. Therefore, viscosity at the time of preparation of a contrast medium and use can be kept constant, and exact diagnosis can be performed.

[0008]

[Embodiment of the Invention]Next, the embodiment of the contrast medium for swallowing function diagnosis concerning this invention is described.

[0009]As a thickening agent used for this invention, for example Guar gum, locust bean gum, Tara gum, xanthan gum, tamarind gum, tragacanth gum, karaya gum, Konjak mannan, CMC sodium, sodium alginate, pectin, Azotobacter BENERANJIGAMU, carrageenan, agar, gellan gum, There are furcellaran, gelatin, curdlan, modified starch, cassia gum, a psyllium seed gum, CMC, methyl cellulose, etc., and a kind may be alone used for these, or two or more sorts may be mixed and used.

[0010]As a contrast medium used for this invention, there is an iodine compound, a barium compound, a gadolinium compound, an iron compound, or a thorium compound. Specifically Iopamidol (Iopamidol), the iohexol (Iohexol), Ioversol (Ioversol), the iomeprol (Iomeprol), Iopromido (Iopromide), the iotrolan (Iotrolan), Ioxaglic acid (Ioxaglic acid), amidotrizoic acid (Amidotrizoic acid), Iotalamic acid (Iothamicacid), yaw DOMIDO (Iodamide), Iotrox acid (Iotrox acid), iodoxamic acid (Iodoxamic acid), Sodium iopodate (Iopodate sodium), iopanoic acid (Iopanoic acid), Barium sulfate (Barium sulfate), iodo pyridone acetic acid (Iodopyridone acetic acid), Iodomethanesulfuric acid (Iodomethane sulfonic acid), Yaw DOHPU rate

(Iodhippurate), iodo meta-mate (Iodomethamate), iodopyracet (Iodopyracet), the amide TORIZO eight (Amidotrizoate), Acetrizoate (Acetrizoate), the METORIZO eight (Metrizoate), Io -- truck mate (Iothlamate) and Io -- and, [ KISHITA ramet ] Io -- glycinate (Ioglicinate) and Io -- and, [ DIPAMIDO ] Io, and, [ GURIKAMIDO ] [ yaw DOKISA mate ] Io -- TOROSATO (Iotroxate) and Io -- and, [ cull mate ] IOKI sag rate (Ioxaglate), the metrizamide (Metrizamide), ioxilan (Ioxilan) and Io -- and, [ BITORIDORU ] Io -- DIKISA Norian (Iodixanol) and thorium dioxide colloid (Thorium Dioxide Colloid). Io -- PIDORU (Iopydol) and Io -- and, [ PIDON ] propyl Yourdon (Propyliodone), tetra iodophthalein (Tetra-Iodophthalein), iodo PINOIKKU acid (Iodoalphinoic acid), and Io -- BANOIKKU acid (Iopanoic acid). Io -- FENOIKKU acid (Iophenoxicacid), [ BUNAMIOJIRU (Bunamiodol) and ] IOPO date (Iopodate) and Io -- BENZAMIKKU acid (Iobenzamic acid). a TAIROPA note (Tyropanoate) and Io -- SETAMIKKU acid (Iocetamic acid). Meglumine gadopentetate (Meglumine Gadopentetate), There are gadoteridol (Gadoteridol), gadodiamide (Gadodiamide Hydrate), ferric ammonium citrate (Ferric Ammonium Citrate), etc.

[0011]The 1st method of preparing such a thickening agent as a fluid holding low viscosity is using together with low viscosity polysaccharide and dissolving in water. low viscosity polysaccharide was chosen from gum arabic, pullulan, soybean polysaccharides, and arabinogalactan here -- it is a kind at least. Even if it dissolves in water at high concentration, viscosity serves as a fluid which was low excellent in mobility, and these polysaccharide has the characteristic that handling is easy.

[0012]That an effect is acquired by the 1st method by making low viscosity polysaccharide into high concentration, The hydrophilic radical which low viscosity polysaccharide has carries out more hydrogen bonds between water, a water molecule is incorporated, a hydrophobic group increases seemingly, and it is presumed for the water molecule which a thickening agent dissolves and becomes the freedom for carrying out a hydrogen bond to decrease. For this reason, although the thickening agent is dissolving rather than powdered voice, it will be freely random spread by the molecule, but while it has been a molecule like a crystal in part, it stops, and it is thought that solution viscosity is stopped low as a result.

[0013]it is a high concentration solution that especially these low viscosity polysaccharide takes effect -- for example, the case of gum arabic -- 3 to 50% of concentration -- it is more desirably considered as 8 to 30% of concentration. When a thickening agent is added as it is the concentration not more than this, viscosity is revealed and mobility worsens, and it cannot maintain at a low viscosity state desirable as a thickener. If concentration of a thickening agent is made low, of course,

the fluid which maintains mobility will be obtained, but it will be inferior to the function of adding to the contrast medium containing moisture and making viscosity reveal. If the above-mentioned density range is exceeded, gum arabic's own viscosity will become large and will become a fluid low thing in itself.

[0014]One or less example and Example 1 by this 1st method are shown. First, it prepared as a liquid thickener by making 10 % of the weight of gum arabic solution which is low viscosity polysaccharide distribute xanthan gum as a thickening agent, making it dissolve in it, and considering it as 5% of the weight of a xanthan gum solution. This prepared thickener was made to reveal viscosity in addition to the JP barium sulfate 100 W/V solution of one 10 times the quantity of this. The result is shown in drawing 1. According to the Example 1, as shown in drawing 1, even if viscosity was revealed and it passed for a long time for a short time, it has checked that viscosity was stable.

[0015]The 2nd method of preparing a thickening agent as a fluid holding low viscosity is using together with reactant ion and dissolving in water. Here, reactant ion is metal ions, such as potassium, calcium, magnesium. Although carrying out the ionic bond of the solution, such as pectin and sodium alginate, to calcium, magnesium, etc., and becoming gel is known, in a little cases, these ion acts in the direction which lowers the viscosity of liquid first. In order to control the reaction of the metal ion of such bivalence, it is also effective to use together sodium acid citrate and sodium metaphosphate for the purpose of a metal blockade.

[0016]Similarly, it is known that potassium will carry out an ionic bond to calcium, magnesium, etc., and will become gel, and chilled water fusibility type carrageenan, for example, sodium and K-carrageenan, acts in the direction which lowers the viscosity of liquid with a little ion similarly. Viscosity can be controlled if salt is added.

[0017]The mechanism which can hold a thickening agent fluid on viscosity according to concomitant use of such a metal ion is as follows. A molecule serves as the shape of a random coil extended freely by solution states, and the thickening agent mentioned above reveals viscosity by carrying out a hydrogen bond to water. If a little existing reactant ion is added here, the flexibility of the molecule of a thickening agent will be lost and a thickening agent will be presumed that it will be restricted with a metal ion and a hydrogen bond with water will be checked. As a result, solution viscosity is stopped low.

[0018]Two or less example and Example 2 by the 2nd method are shown. First, it prepared as a liquid thickener by making 4% of the weight of a salt solution distribute chilled water fusibility type carrageenan, making it dissolve in it, and considering it as

15% of the weight of a chilled water fusibility type carrageenan solution. This prepared thickener was made to reveal viscosity in addition to the JP barium sulfate 100 W/V solution of one 10 times the quantity of this. The result is shown in drawing 1.

According to the Example 2, as shown in drawing 2, even if viscosity was revealed and it passed for a long time for a short time, it has checked that viscosity was stable.

[0019]The method of using a thickening agent together with low-molecular sugar, and dissolving in water as application of the 1st method, is also used. For example, a thickening agent can be held in the low viscosity state by dissolving sugar, liquid sugar, or sugar-alcohol with a thickening agent at high concentration. Example 3 of this method is shown below.

[0020]Example 3 -- it prepared as a liquid thickener by making the sorbitol solution of 60% of the viscosity which is low molecule sugar distribute tara gum, making it dissolve in it first, and considering it as 10% of the weight of a tara gum solution. This prepared thickener was made to reveal viscosity in addition to the JP barium sulfate 100 W/V solution of one 10 times the quantity of this. The result is shown in drawing 3.

According to the Example 3, as shown in drawing 3, even if viscosity was revealed and it passed for a long time for a short time, it has checked that viscosity was stable.

[0021]As for the thickener made by the above method, it is preferred that it is a thing as for which below equivalent weight adds to a contrast medium and which makes viscosity or gelling reveal. That is, in order to use auxiliary for the purpose of thickening to a contrast medium, it is meaningful as contrast-medium addition liquid with auxiliary the effect of viscous increase being larger than the effect of low-viscosity-izing by an equivalent amount of the amount used being diluted twice when it is desirable that it is the following and it moreover adds in equivalent amount. As auxiliary addition liquid, it is fully low viscosity at the time of use, and when it adds to a contrast medium, it is preferred in other words, that it is easily spread in the whole and viscosity is revealed rather than an undiluted solution.

[0022]The reason with preferred adding the thickener by this invention below in equivalent weight to a contrast medium is for not spoiling the original function of a contrast medium. In this meaning, a direction with as much as possible little amount used is good. However, in order to attach viscosity and gelling to a contrast medium in a small quantity, it is not preferred that the viscosity of a liquid thickening agent becomes large and mobility worsens. What carries out the distributed dissolution easily to a contrast medium, and reveals viscosity and gelling for a short time is good, and it is preferred that the volume ratio to a contrast medium is chosen in consideration of these.

[0023]As for the thickener concerning this invention, it is preferred on use to be subdivided into either a portion container or a small bag. The thickener concerning this invention is divided and prepared for the first liquid and the second liquid, adds these first liquid and second liquid to a contrast medium, and can make viscosity or gelling reveal by the interaction of the first liquid and the second liquid. For example, the first liquid and the second liquid are used as a different thickening agent solution, thickening agents react in such combination, and it is made to produce thickening or coagulation. Or the first liquid is used as a thickening agent solution, and it is made to thicken or solidify with such combination as a solution containing the ion which has reactivity to the thickening agent of the first liquid in the second liquid.

[0024]Specifically A carrageenan solution, a locust-bean-gum solution and a carrageenan solution, and a potassium chloride solution, Combination, such as a xanthan gum solution, a locust-bean-gum solution and a xanthan gum solution, a guar gum solution and a pectin solution, a solution containing calcium ion, and sodium alginate and a solution containing calcium, is effective.

[0025]It is preferred to use the container which carries out the subdivision package of 2 liquid like a DISU pen pack, and can perform simultaneous extraction at the time of use as a method of adding 2 liquid to a contrast medium simultaneously.

[0026]Example 4 using example 4 2 liquid is shown below. The first liquid is 14% of the weight of the solution with which an equivalent amount of LM pectin and sodium acid citrate were mixed, and the second liquid is 7 % of the weight of calcium lactate solution. The distributed dissolution of first liquid 30 weight section and the second liquid 20 weight section was carried out at JP barium sulfate 100 W/V solution 100 weight section, and viscosity was made to reveal. The result is shown in drawing 4. According to this example, as shown in drawing 4, even if viscosity was revealed and it passed for a long time for a short time, it has checked that viscosity was stable.

[0027]A comparative example, next the comparative example which added the powdered thickener of conventional pregelatinized starch to the contrast medium are shown. 10 g of pregelatinized starch was added in a 100-g JP barium sulfate 100 W/V solution, and viscosity was made to reveal. The result is shown in drawing 5. As shown in drawing 5, the thing using pregelatinized starch as a thickener has the slow manifestation of viscosity compared with the above-mentioned example, and it turns out that viscosity is not stabilized.

[0028]Deglutition diagnosis was given to the floor-of-mouth malignant tumor patient of a reconstruction after the operation instance by the surgical removal of the tumor and the forearm skin flap using the contrast medium made to reveal by the 1st method



of the above. Since this patient had favorable recovery of a wound surface etc., drinking water training was started after progress of an one week after the operation for the purpose of changing from the nutrition management by a nasotracheal tube to an ingestion. however, intense -- being able to steam and being crowded -- etc. -- ingestion of water was impossible. When the deglutition moving state of barium water was observed under VF, misswallowing of barium water was accepted by pharynx \*\*\*\*\* and the sending incompetence by a tongue. Then, when mixed a 6-g xanthan gum solution in barium water 50%, viscosity was made to reveal and it was made to swallow, it was able to swallow, without carrying out misswallowing. The water which added the xanthan gum solution 12g in which the same viscosity is obtained from this result was used for deglutition training, and rehabilitation of the swallowing function was performed.

[0029]

[Effect of the Invention]As mentioned above, according to this invention, the thickener for contrast media which can reveal viscosity or gelling so that the change with time of the viscosity of the contrast medium which changed into the gelling state may decrease can be provided.

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## DESCRIPTION OF DRAWINGS

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[Brief Description of the Drawings]

[Drawing 1]It is a figure showing the change with time of the viscosity of the contrast medium using the thickener (example 1) which consists of a xanthan gum solution which used gum arabic together.

[Drawing 2]It is a figure showing the change with time of the viscosity of the contrast medium using the thickener (example 2) which consists of chilled water fusibility type carrageenan which used the salt solution together.

[Drawing 3]It is a figure showing the change with time of the viscosity of the contrast medium using the thickener (example 3) which consists of a tara gum solution which used the sorbitol solution together.

[Drawing 4]It is a figure showing the change with time of the viscosity of the contrast medium using the thickener (example 4) which consists of the sodium-acid-citrate solution and calcium lactate solution of LM pectin.

[Drawing 5]It is a figure showing the change with time of the viscosity of the contrast

medium using the thickener (comparative example) which consists of pregelatinized starch.

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